EFFICACY OF DERMABRASION ALONG WITH 1% TOPICAL 5-FLUOROURACIL IN 25 PATIENTS OF VITILIGO

Dissertation submitted in partial fulfillment of regulation for the award of M.D. (Dermatology, Venereology and Leprology) Branch - XII

THE TAMILNADU

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CERTIFICATE

This is to certify that the dissertation entitled" **Efficacy Of Dermabrasion Along With Topical 1% 5 -Fluorouracil In 25 Patients Of Vitiligo**" is the bonafide original work of Dr.A.P.Balaji in partial fulfillment of the requirements for MD DERMATOLOGY, VENEREOLOGY& LEPROLOGY BRANCH XII examination of the Tamilnadu Dr.MGR Medical University to be held in April 2012.The period of study was from June 2010 to June 2011.

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DECLARATION

I **Dr. BALAJI A.P** solemnely declare that the dissertation entitled "**EFFICACY OF DERMABRASION ALONG WITH TOPICAL 1% 5 - FLUOROURACIL IN 25 PATIENTS OF VITILIGO**" is a bonafide work done by me at Coimbatore Medical college Hospital during the year June 2010- June 2011 under the guidance & supervision of Dr.P.P.Ramasamy M.D.,D.D., Professor & Head of Department, Department Of Dermatology, Coimbatore Medical College& Hospital.

The dissertation is submitted to Dr MGR Medical University towards partial fulfillment of requirement for the award of MD degree branch XII Dermatology, Venereology& Leprology.

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CONTENTS

EFFICACY OF DERMABRASION ALONG WITH 1% TOPICAL 5 FLUOROURACIL IN 25 PATIENTS OF VITILIGO.

ABSTRACT :

BACKGROUND : Vitiligo is a common pigmentary disorder of the skin with much prejudice and taboos.Various therapeutic approaches are available at present, which includes topical and systemic steroids, photo chemotherapy with psoralens, narrow band UVB therapy, and calcineurin inhibitors. In addition to medical therapies various surgical procedures are available for patients with stable vitiligo. Among the various surgical modalities, therapeutic dermabrasion with topical 5- fluorouracil application over stable vitiligo patch had shown good results in a short duration in various studies, either alone or in combination and seems to be have less side effects.**AIM OF THE STUDY** :To evaluate the efficacy of dermabrasion with topical 1% 5-fluorouracil in patients with stable vitiligo patches and to assess the feasibility of this procedure in day to day practice**.** **METHODOLOGY** : This was one year prospective study done on twenty five patients attending Department of Dermatology at Coimbatore

Medical College Hospital, Coimbatore .Both men and women of age ranging from 15-60 years of with clinical diagnosis of stable vitiligo of more than 2 year duration were included in the study. Patients with actively spreading vitiligo , those with acrofacial and mucosal vitiligo, pregnant and lactating women , childrens, diabetic patients, those currently undergoing other topical or systemic therapy for vitiligo, patients with history of keloidal tendency ,bleeding diathesis and koebner phenonmenon were excluded from the study. The procedure of dermabrasion with topical 5 fluorouracil was done for these patients in first 6 months ,with follow up of the patient for next 6 months. **RESULT:** At the at the end of 6 months, out of 25 patients 4 did not turn for follow up. Partial repigmentation was observed in six patients (28.6%) and total repigmentation in fifteen patients(71.4%). **CONCLUSION**: Dermabrasion along with topical 5 fluorouracil can be used as a simple office procedure, in repigmenting localised stable vitiligo, which is very economical & brings early regimentation without any significant side effects.

Key words : Dermabrasion ,5 Fluorouracil, stable vitiligo.

INTRODUCTION

Vitiligo is a common pigmentary disorder of the skin with much prejudice and taboos. Most of the time confused with leprosy and brings embarrassment for the patient even though the life expectancy remains unaffected.

The exact etiology of the disease is not known. Various therapeutic approaches are available at present, which includes topical and systemic steroids, photo chemotherapy with psoralens, narrow band UVB therapy, immuno modulators and calcineurin inhibitors.

In addition to medical therapies various surgical procedures are available for patients with stable vitiligo since 1964.

In case of vitiligo, there is a partial or total destruction of melanocytes. The prime aim of various medical and surgical therapies is activation of the reservoir melanocytes of hair follicle.

The main aims of the surgical procedures are:[1]

- The melanocyte stimulation resulting in proliferation, migration and re-pigmentation from the hair follicles towards the lesion.
- Introduction of artificial pigments into the lesions.
- Repopulation of the depleted melanocytes by various grafts.

Among the various surgical modalities, therapeutic dermabrasion with topical 5- fluorouracil application over stable vitiligo patch had shown good results in a short duration in various studies, either alone or in combination and seems to be have less side effects.

Review of Literature

REVIEW OF LITERATURE

VITILIGO:

Vitiligo is an idiopathic, acquired, circumscribed hypomelanotic skin disorder, characterized by milky white patches of different sizes and shapes and affects 1-2% of the world population. [2, 3]

Historical Aspects:

The earliest reports on patchy skin diseases date back approximately 1500 BC. The Roman physician Celsus was the first to coin the term Vitiligo in his Latin medical classic De Medicina in 1st century AD. El Mofty suggests that vitiligo is derived from the Latin word 'Vitelius' which means 'calf' referring to the characteristic white patches of the disease resembling the white patches of a spotted calf. [5] Other authors however believe that the term is derived from the Latin word'vitium' meaning a fault or blemish. [4]

The Ancient Indian sacred book, 'Atharva Veda' reports on the disease in the name called" kilas "meaning "white "The Indian Manu Smirti (200BC) describes "Sweta Kushta " meaning white disease which probably represents vitiligo. [5]

In Bible the white spots were described in the Old Testament under the Hebra word 'Zora at', and this word was translated as 'lepra' in the Greek. [6]

In South India, vitiligo is still called 'Ven Kushtam' translated as 'white leprosy'. As the social stigma makes patient conceal their white spots, even today in the Indian Villages, the disease is often called 'Charak' meaning 'the secret disease'.

EPIDEMIOLOGY

Vitiligo is relatively common disorder affecting all races around the world. [7] Even though it does not show sexual predilection the female prevalence in some studies probably has been attributed to the greater concern about their cosmetic defect. [8] Its incidence varies between 1-2% over the world population. [9]

In India, highest number of cases has been reported in the states of Gujarat and Rajasthan.[10] Few dermatological outpatient records shows, the incidence of vitiligo to be 0.25-2.5% in India .[11] Vitiligo appears to be observed more commonly in darker skin types.

The mean age of onset of vitiligo is 25 years for males & 20 years for females.[12]About 20% of vitiligo patients have atleast one first degree relative with vitiligo. The relative risk for 1 st degree relatives is 7 -10 fold.[13]

AETIOPATHOGENESIS

The etiology of vitiligo is multifactorial with a complex pathogenesis. Although several theories have been proposed to explain the loss of epidermal melanocytes in vitiligo, the precise cause remains unknown. Considerable progress has been made, however over the last two decades.

GENETIC FACTORS AND INHERITANCE

Vitiligo is a disease of polygenic origin with incomplete penetrance involving multiple genes and environmental triggers. Recently multiple susceptibility loci and genetic heterogeneity have been identified. The inheritance may involve genes associated with melanin biosynthesis, response to oxidative stress, and regulators of autoimmunity.

The possible HLA associations with vitiligo in more than one study include HLA A2, DR4, DR7, Cw6, HLA DRB1A *04-(DQA1*0302)-DQB1*0301 and A25-Cw*0602-DQA1*0302. [14, 15, 16]

A positive family history has been observed in 30-40% of vitiligo patients suggesting a genetic basis for this disorder.[17] It has also been reported in monozygotic twins.

Several susceptibility genes have now been identified, including loci in the MHC, PTPN22, and NALP1 for generalized vitiligo vulgaris. One of the best candidate gene identified, known as FOXD3 ("Forkhead box" D3) located on chromosome 1 (1p32–p31) is a transcription factor that suppresses melanoblast development from the neural crest [18]. when dysregulated in the form overexpression might harm melanocytes.

THEORIES ON THE PATHOGENESIS:

Many factors play a role in etiopathogenesis in addition to genetic predilection. Traditionally there have been three hypotheses to explain vitiligo. [19]

1. Autoimmune Theory
2. Neural Hypothesis
3. Self destructive Theory

1. AUTOIMMUNE THEORY

This is most popular hypothesis proposed for pathogenesis of vitiligo it states that melanocytes are killed by autoimmune effector mechanism, probably there may be some kind of biochemical trauma to melanocytes resulting in the release of some antigenic substances and subsequent auto immunization or there may be certain immune cells directed against antigenic components of autologous melanocytes**.**

The various evidences to suggest autoimmune hypothesis are

- The clinical association of vitiligo with a number of auto immune disorders like autoimmune Thyroid disease ,Diabetes mellitus, Pernicious anaemia, Addison's disease, Hypoparathyroidism, Myasthenia gravis and Alopecia areata [20,21,22] .

- Generalized vitiligo is a component of the APECED (APS1) and Schmidt (APS2) multiple autoimmune disease syndromes.

Role of Humoral immunity

- Several circulating autoantibodies to non-pigment cell antigens (common tissue antigens), cytoplasmic pigment cell antigens, and pigment cell surface antigens [23] have been found in sera of vitiligo patients.

- Organ-specific autoantibodies to thyroid, gastric parietal cells and adrenal tissue are found in the serum more frequently in patients with vitiligo than in the general population

- A complement-fixing antibody to melanocytes has been found in the serum of several patients who in addition to vitiligo had alopecia areata, mucocutaneous candidiasis and multiple endocrine insufficiencies

- Antimelanocyte antibody dependent cellular cytotoxicity and complement mediated lysis have been noted in vitiligo patient. [24]

- Injections of serum IgG fractions from patients with vitiligo found to have a destructive effect on melanocytes of the human skin grafted onto nude mice.[25]

- The serum level of auto antibodies was found to correlate with the disease activity and the extent of the cutaneous depigmentation

Role of Cell mediated immunity

In a recent study on skin lesions of vitiligo a high frequency of cutaneous lymphocyte antigen-positive-activated cytotoxic T-cells clustered in perilesional skin in the vicinity of disappearing melanocytes have been noted.[26]

Increased levels of CD45RO memory T-cells, soluble interleukin-2 receptors and expression of the cutaneous lymphocyte antigen in infiltrating T-cells, suggest an activation of circulating T-cells and their recruitment to the vitiligo skin.[27, 28, 29]

Immunotherapy of melanoma with high-dose IL-2 therapy, infusion of peptide pulsed dendritic cells, and MelanA/MART-1 specific CTL clones [30] produced vitiligo-like depigmentation suggesting a cytotoxic T cell activity over melanocytes.

2. NEURAL HYPHOTHESIS

This hypothesis suggests that destruction of melanocytes may occur because of liberation of some unusual neurochemical mediator or due to a gross alteration in the ratio of the normal neurotransmitter substances in the lesion.

Evidences in favour of neural hypothesis include

- Occurrence of Vitiligo in neurologically compromised skin, following peripheral nerve injury, with multiple sclerosis , following viral encephalitis, with Horner's Syndrome, and among emotionally hyper stressed and psychiatric patients.[31, 32]
- Dermatomal distribution of segmental vitiligo.
- An increased immunoreactivity of neuropeptide (NYP) or an altered balance of nerve growth factor receptors and calcitonin gene related peptide has been observed in vitiligo

- The common embryologic origin of melanocytes and the nervous system.
- Demonstration of direct contact between cutaneous free nerve endings and epidermal melanocytes in vitiligo macules.
- Repigmentation in segmental lesions was observed by administration of nilamide, an oral monoamine oxidase inhibitor, to suppress metabolism of catecholamines at the sympathetic nerve endings.

3. SELF DESTRUCTIVE THEORY

This theory suggests that precursors or metabolites of the melanogenesis are toxic to melanocytes. Melanocytes may possess an intracellular protective mechanism to eliminate toxic melanin precursors (e.g. dopa, dopachrome, and 5.6dihydroxyindole)) and free radicals. In case of vitiligo, there might be a disturbance of this mechanism,, leading to an accumulation of indoles and free radicals causing destruction of melanocytes.[33]

One other possible mechanism could be damage to the membranes of melanosomes by genetic mechanisms or by perioxidation [34,] which prevent leakage of these compounds into the cellular milieu [35, 36] causing destruction of melanocytes.

OTHER HYPOTHETICAL THEORIES

- **MELANOCYTE GROWTH FACTOR REDUCTION HYPOTHESIS**

Depigmentation in vitiligo may be due reduced local and circulating levels of growth factor responsible for normal proliferation and maintenance of melanocytes. [37]

- **MELANOCYTE DEFECTIVE ADHESION HYPOTHESIS**

Repeated friction in non-lesional skin of vitiligo patients induces detachment and transepidermal elimination of melanocytes [38] that could have

been previously damaged by another process,[39] suggesting that minor mechanical trauma in non-lesional vitiligo skin is probably the cause of depigmentation .

- **ANTIOXIDANT DEFICIENT THEORY**

Melanocyte toxicity can occur following a breakdown in antioxidant defence of epidermis. [40] This theory is supported by the observation in the epidermis of vitiligo patients of low levels of catalase activity. This oxidative stress could lead to accumulation in skin of high concentrations of 6 and 7 biopterins which inhibit the tyrosinase activity extremely cytotoxic to melanocytes. [41]

COMPOSITE HYPOTHESIS

This hypothesis suggests that vitiligo is not a single disease but involves several processes. This includes

1. Excessive acetyl choline production in skin or decreased cholinesterase activity in skin
2. Process of self destruction caused by metabolites evolved during melanin synthesis
3. An autoimmune phenomenon

DISORDER OF MELANOCYTE SURVIVAL

Several observations suggest the involvement of melanocyte apoptosis and the SCF/c-kit/MITF/Bcl-2 pathway in the pathogenesis of vitiligo. Decrease in Bcl-2 expression of melanocytes, reduced levels of SCF, down-regulated expression of c-kit and MITF-M proteins has been reported in the perilesional skin of vitiligo patients.[42, 43]

INTRINSIC DEFECT

An intrinsic defect of the structure and function of rough endoplasmic reticulum in vitiligo melanocytes.[44]

CLINICAL FEATURES [45]

A typical lesion is a well defined depigmented (milky white or chalky) macule, round to oval in shape, showing a variable number of depigmented (white) hairs, without any change in the skin texture. In many cases the margin is hyperpigmented.

The location of individual macules, their number, size and shape varies widely. The initial macules usually occur on the exposed areas (such as the dorsal surface of hands, elbows, feet, legs, knees, neck and face), body folds (such as axillae, groin, and sub mammary region in women), lips and genitalia. Involvement of pretibial region, palms and sole are quite common in India.

In the covered areas, the initial lesion is commonly noted on the chest wall, lower back or areola and the lesion may be one or more macules widely varying in size and shape. Distribution is generally more or less symmetrical when lesions occur bilaterally.

In some cases almost total depigmentation of body surface may develop slowly or rapidly with only a few or no islands of normal pigmentation. The lesions enlarge by invading the normally pigmented surrounding skin, which assumes a concave shape at the border. Virtually no area of skin is exempted.

The initial unifocal lesion may be followed by the appearance of new lesions elsewhere. In less than 25% of cases the onset may be multifocal. Onset of the lesions is usually insidious. The disease is usually progressive in nature but the course is virtually unpredictable.

While some lesions may show signs of repigmentation, new lesions may develop on other parts of the body simultaneously. There is an episodic phase of rapid extension of lesions after remaining quiescent over a long period of time.

Koebner's phenomenon is seen in 6-20% of cases of vitiligo Vulgaris. [46] Minor trauma such as scratch mark, laceration, or stitches on the skin results in

the development of a corresponding linear depigmented macule, usually in 2-4 week.

Morphological variations on the typical vitiligo macule. [47]

- Trichrome vitiligo: characterized by hypopigmented and depigmented macule in addition to normally pigmented skin.
- Quadrichrome vitiligo:besides the three colours of trichrome vitiligo. Here the fourth colour is macular perifollicular or marginal hyperpigmentation.
- Pentachrome vitiligo: blue-gray hyperpigmentation in addition to four colours of quadrichrome vitiligo representing melanin incontinence.
- Blue vitiligo corresponds to vitiligo macules occurring in sites of post inflammatory hyperpigmentation.
- Inflammatory vitiligo has an erythematous, raised border.
- Confetti macules or vitiligo ponctue: these are tiny discrete hypomelanotic macules that may occur randomly or it may be perifollicular.
- Valeceo' type of vitiligo: very sudden rapid onset, extension and spread of lesion following emotional trauma and repression.

Classification of vitiligo (according to Ortonne, 1983)[48]		
Localized vitiligo	**Generalized vitiligo**	**Universal vitiligo**
1.. Focalis; only one or more depigmented macules not in a segmental or zosteriform distribution **2.. Segmental: one or more macule in a quasidermatomal pattern** **3.. Mucosalis: only mucous membrane(s) affected**	**Acrofacial: Distal extremities and face** **Vulgaris: scattered macules over the entire body with a symmetrical distribution pattern** **Mixed :Acrofacialis and/or vulgaris and/or segmentalis**	**Universalis: > 80 % depigmentation**

Clinical Types of Vitiligo [49]

- **Generalized vitiligo / Vitiligo vulgaris**: This is the most common type of vitiligo and is characterized by few to many widespread macules. These macules are often symmetrically placed and involve extensor surfaces of the trunk, extremites, periorificial areas and mucous membranes.
- **Focal vitiligo / Vitiligo areata** is an isolated macule or a few scattered macules, limited in both size and number.
- **Segmental / Dermatomal / Zosteriform Vitiligo**: characterized by unilateral vitiligenous macules and patches with early age of onset stable course, frequent association of leukotrichia ,absence of koebner phenomenon, and less response to PUVA therapy. [50] Trigeminal areas are involved in > 50% of cases.
- **Acrofacial vitiligo** involves distal digits and peri-orificial facial areas.
- **Lip – tip vitiligo**: Periungual involvement occurring with involvement of mucous membranes like lips, distal penis and nipples.
- **Vitiligo universalis / Universal vitiligo**: widespread vitiligo with few remaining areas of normal pigmentation.

Childhood vitiligo: [51]

The characteristic features of vitiligo in children are

- A positive family history,
- Fewer lesions,
- Less than 5% of body surface area involvement,
- Frequent segmental involvement, and
- Greater difficulty in treatment but relatively better prognosis

Differential diagnosis:

- Postinflammatory Hypopigmentation
- Idiopathic guttate hypomelanosis
- Indeterminate Hansen
- Pitryasis Alba
- Nevus Anemicus
- Nevus Depigmentosus
- Chemical Leukoderma
- Piebaldism
- Albinism
- Ash Leaf Macule
- Halo Nevus
- Hypopigmented mycosis fungoides
- Post Kala Azar Dermal Leishmaniasis
- Hypomelanosis of Ito
- Waarden Burg's Syndrome
- Chediak-Higashi syndrome
- Woolf's Syndrome
- Syphilis & Yaws

PRECIPITATING FACTORS:

Endogenous factors:

- Genetic factors
- Physical and emotional stressful events(puberty, pregnancy, menopause, febrile illness)
- Associated internal disorders
- Associated skin diseases

Exogenous factors:

- Chemicals(film developers , rubber , quinones and bleaching agents)
- Drugs (such as beta adrenergic blocking agent) [52]
- Physical stimuli (koebner phenomenon): scratching, bumping, stubbing, grazes and burn.

COURSE OF THE DISEASE

The natural course is uncertain, often showing tendency towards slow progression. Spontaneous repigmentation is noted in about 10-20% of patients, most frequently in un-exposed areas and in younger patients.

Focal vitiligo, although stable for a time, may be a precursor of generalized vitiligo but spontaneous resolution is possible.

The course of vitiligo vulgaris is often abrupt onset, followed by progression for a time,then a period of stability follows and may last for some time, even decades. This may be followed later by a period of rapid progression. Total spontaneous regression is unusual.

Segmental vitiligo slowly progress for a relative period of one year and remains stable with little extension or regression. Tendency towards spontaneous pigmentation is rare.

PROGNOSIS:

The following factors usually indicate a poor prognosis:

1. Lesions on the resistant sites, such as
    - Bony prominences
    - Non fleshy areas
    - Non-hairy areas
    - Mucosal areas
2. Family H/O vitiligo
3. Old age
4. Associated with systemic diseases
5. Higher percentage of white hairs in the patch
6. Extensive long standing cases
7. Injudicious administration of topical and systemic medications particularly chemotherapeutic agents. [53, 54, 55]

Vitiligo disease activity score (VIDA) [56]

It is a six-point scale for assessing vitiligo activity and the scoring is based on the individual's own opinion of the present disease activity over time. Active vitiligo involves either expansion of existing lesions or appearance of new lesions. Grading is as follows:

+4 – Activity of 6 weeks or less duration;

+3 – Activity of 6 weeks to 3 months;

+2 – Activity of 3 - 6 months;

+1 – Activity of 6 - 12 months;

0 - Stable for 1 year or more; and

-1 - Stable with spontaneous repigmentation since 1 year or more.

- A low VIDA score indicates less activity.
- For vitiligo surgeries to be performed, the VIDA score must be 0 or -1 [57]

Inflammatory and autoimmune diseases associated with vitiligo

- Thyroid disorders (Hashimotos thyroiditis, Graves' disease, toxic thyroiditis) [58, 59] seen in 0.6 % -38% of patients.
- Diabetes mellitus: occurs in 1 to 1.7% of vitiligo patients and conversely, vitiligo occurs in 4.8% of diabetic patients.[60]
- Alopecia areata
- Rheumatoid arthritis
- Addison's disease
- Pernicious anaemia
- Psoriasis
- Systemic lupus erythematosus
- Autoimmune Polyendocrine Syndromes

Rare associations:

- Lichen Planus.
- Lichen Sclerosus
- Urticaria
- Ichthyosis
- Malignant Melanoma
- Human Immunodeficiency Virus Disease
- Bullous pemphigoid,
- Dermatitis herpetiformis
- Twenty nail dystrophy
- Halo naevi

Associated hair abnormalities:

- Leukotrichia: Depigmented hairs are found commonly in isolated vitiligo macules, it has been reported in 9-45% of vitiligo patients which is a marker of poor prognosis
- Premature gray hair occurs in up to 37% of patients. [61]

Ocular Abnormalities

Ocular abnormalities include uveitis, iris transillumination defects and heterochromia irides retinal pigment epithelium hypopigmentation and depigmentation, chorio retinal scars, pigment clumping, retinitis pigmentosa.[62]

Vogt-Koyanagi-harada syndrome: (Uveomenigitic syndrome)

A rare multisystem disorder with acute onet of severe uveitis, meningo encephalitis and deafness, followed by the appearance of poliosis,, alopecia areata and vitiligo

Otic abnormalities

- Alezzandrini's syndrome: unilateral retinal degeneration, ipsilateral vitiligo, poliosis, and deafness.
- Sensory neural deafness has been reported in a very few patients with vitiligo [63]

Laboratory evaluation of patients with vitiligo:

Histopathology:

Histopathological findings in vitiligo differ according to the three phases of the disease: [64, 65]

(1) Early stage lesions,

(2) Established lesions and

3) Long standing lesions

Early stage lesions:

Superficial perivascular infiltrate of lymphocytes with a variable number of lymphocytes in the lower half of the epidermis is seen. . This can be mistaken for a series of other cutaneous inflammatory lichenoid/spongiotic disorders.

Established vitiligo:

There is an absence of pigmentation of the basal epidermal layer. Fontana masson silver stain confirms the absence of melanin. [66] There may be a sparse superficial perivascular infiltrate. Histochemical studies show a loss of DOPA-positive melanocytes in the basal layer.

Long-standing lesions:

A marked absence of melanin in the epidermis is the main finding. Inflammatory infiltrates cannot be demonstrated. Degenerative changes are seen, besides degenerative changes in nerves and sweat glands.

Progressive lesions:

The content of melanin in the epidermal basal layer may be either reduced or normal. Lymphocytes sometimes can be found in close apposition to melanocytes at the advancing edge of the lesion.[67]

Findings in perilesional and distant areas:

Focal areas of vacuolar degeneration in the basal layer, in association with a mild mononuclear cell infiltrate, have been observed in clinically normal pigmented skin adjacent to vitiliginous areas. [68]

Micro depigmentation:

Microscopic disappearance of melanocytes, in association with T-cell infiltrates in the dermoepidermal junction of the clinically normal- pigmented skin in patients with active generalized vitiligo [68] has been recently described.

Special stains for melanin

- Fontana-Masson stain
- Silver nitrate [69]

The DOPA Reaction:

On the basis of DOPA reaction vitiligo may be classified as follows: [70]

Absolute : No DOPA positive melanocytes

Relative type 1 : Weak DOPA reaction but normal number of melanocytes

Relative type 2 : Reduced number of DOPA positive melanocytes

Immunohistochemical staining for melanocytes:

Immunohistochemical stains used for finding melanocytes are S-100 protein, HMB 45, NKI-beteb , T311 ,MEL-5(clone TA99) and Melan-A(A-103)/Mart-1. [71,72,73]

MANAGEMENT OF VITILIGO

It can be divided in to Medical therapy and Surgical therapy

Medical therapy includes

- General measures
- Topical therapy and
- Systemic therapy

GENERAL MEASURES

- Counselling the patient regarding the nature of the disease, its course and prognosis.
- Reassurance is essential.
- Avoidance of precipitating factors.

TOPICAL THERAPIES

- Corticosteroids:

  Mid to super potent steroids can be tried upto 2 to 4 months

  Interrupted topical therapy:

To minimize complication especially for lesions around the eyelids, steroid ointment can be applied twice daily for 2 months followed by a treatment free period of 2 weeks in cyclical order that can be continued for 8 months or longer if there is a response.

- Calcipotriene :

  Once daily application increases the efficacy of topical steroids.

- Tacrolimus ointment:

  0.1% ointment found to be efficacious mainly in case of mucosal vitiligo.

- Topical PUVA:

  0.05%-0.1% 8-Methoxy Psoralen followed by UVA can be used.

- Human Placental Extract:

  It is a hydro alcoholic extract of the human placenta 95% ethanol.[74] Melagenina should be applied three times a day before exposure to ultraviolet light, sunlight or infrared light. The timing of the application is said to be critical and must be administered at 8 hour intervals. The treatment duration varies between months to as long as 10 years.

- Basic fibroblast growth factor :
  - Recently developed treatment modality capable of stimulating the melanocytes from the hair follicles & also act as chemotactic agents to direct the new melanocytes to vitiligo patch.[75]

- Topical application of pseudocatalase and calcium chloride with short term UVB used twice a day has been claimed to produce repigmentation.

- Calcipotriol with PUVA therapy:

  It has been reported to be an effective adjunctive treatment for vitiligo enhancing the efficacy of PUVA therapy.

SYSTEMIC THERAPIES

Photochemotherapy:

This is the most widely employed systemic therapy for vitiligo. Treatment involves intake of psoralen derivatives or any other photosensitizing agent orally, followed by irradiation with Ultraviolet A.

PUVA

Among the furocoumorin compounds, psoralen is the most effective one. The exact mechanism of pigmentation following PUVA is not fully known. Increase in number of functional melanocytes; number and size of melanosomes, number of dendrites of melanocytes, transfer of melanosomes to keratinocytes and tyrosinase activity have been noted.

TYPES OF PSORALENS

- TRIMETHYL PSORALEN (TMP)
- 8 METHOXY PSORALEN (8-MOP)
- 5METHOXY PSORALEN

ORAL PUVA

Psoralens (8-MOP or TMP) are given in the dose of 0.6mg/kg/day followed by exposure to UVA after 1-3 hrs for 2-3 times a week. The treatment is started with a initial dose ranging from 0.5 to 5J/cm2 of UVA based upon minimal erythema dose or skin type. Subsequently increments of 0.5J/cm2 are made till a uniform erythema occurs over the lesions or a total dose of 8J/cm2 is reached.

If sunlight is utilized as a source of UV light the TMP is preferred as it is less phototoxic when compared to 8-MOP.[76] If there is no response after 6 months or 50 treatments, PUVA should be terminated.

CONTRAINDICATIONS:

- It should be avoided in less than 12 years of age.
- Pregnancy
- Lactation
- Photosensitivity
- Radiotherapy
- Porphyrias
- Systemic lupus erythematosus.

Side effects

- Nausea
- Pruritus
- Epigastric tenderness
- Insomnia
- Erythema
- Skin rash

NARROW BAND UVB

Narrow band UVB obviates sun burn and phototoxicity produced by broadband UVB and it is more effective than PUVA in terms of repigmentation.

Mechanism of action:

By means of immuno modulation and stimulation of the melanocyte reserves in the hair sheaths, it produces repigmentation of vitiligo patch. [77]

ADVANTAGES

- Since there is no oral intake like psoralen, no systemic side effects are noted.
- It can be used in pregnancy and childhood. [78]
- Exposure time is shorter than PUVA.

Duration of therapy:

Given twice weekly has become the preferred therapy for vitiligo. If no response is observed after 6 months further therapy should be discouraged.

Systemic corticosteroids:

It can be used alone or in combination with topical agents for vitiligo mainly used in controlling the activity of the disease.

Oral Mini Pulse therapy (OMP).

Smaller cyclical pulsed administration of corticosteroids mainly used for halting rapidly progressive vitiligo. [79]

It comprises of administering 5mg of betamethasone/dexamethasone with breakfast on two consecutive days in a week. For children, the dosage is 0.5mgfor every 5kg of body weight. For those who do not respond to 5 mg/day, 7.5 mg/day may be used, and then reduced to 5 mg/day if disease progression is arrested.

OMP is not useful to repigment stable vitiligo patches. Optimal duration of therapy to stop vitiligo progression varies between 3 to 6 months.

Oral prednisolone 10-40 mg/day for a period of 3months to 1 year and Systemic therapy with ACTH[80] (25-40 IU IM twice a week) has been tried in vitiligo with good results

KHELLIN (KUVA)

Khellin is extracted from the seeds of the plant Ammi visnaga. It is a furanochrome with a chemical structure closely resembling the psoralen family and having similar photobiological,photochemical and phototherapeutic properties.[81,82]

Can be given at the dose of 50- 100 mg, two and half hours prior to exposure to sunlight. UVA can be given at the dose of 15 J /Cm2 .Side effects include a mild elevation of liver enzymes, nausea & orthostatic hypotension[83] and porphyria cutanea tarda.[84]

PHENYLALANINE

It is a natural, essential aminoacid and a precursor of tyrosine which is required for the synthesis of melanin. Prescribed dose is 50 mg/ kg body weight, 45 minutes prior to UV exposure twice a week. [85]

CONTRAINDICATIONS

- Phenylketonuria
- Skin cancer
- Impaired liver and renal function
- Pregnancy
- Lactation
- Arsenic exposure

Vitamins and Trace Elements:

2 mg of folic acid and 500 mg of vitamin C twice a day along with 100 mg of vitamin B12 every 2 weeks administered intramuscularly showed significant repigmentation in patients of vitiligo.[86] Vitamin C and E are used in vitiligo for its antioxidant property.

Heliotherapy:

It is usually combined with treatments like topical steroids or ingestion of various vitamins. Exposure to the sun can be done with psoralens, melagenina, khellin and phenylalanine. The mode of action is unknown but it may re-establish the normal tyrosinase activity possibly by reducing serum copper level and plasma ceruloplasmin. [87]

ANAPSOS

It is made of an extract of algae plant claimed to bring repigmentation in few patients of vitiligo.[88]

ANTIOXIDANTS

Canthaxanthine

A food colouring agent used as a pigment to darken and to photo protects vitiliginous skin. [89] Intake can produce yellow deposits in the retina which have been seen to persists after 30 years of stopping the drug.

Alfa Tocopherol

Combined with weak to moderate topical corticosteroids or PUVA. It has been proposed for treatment for vitiligo with little success. [90]

IMMUNOMODULATORS:

- Cyclophospamide

  Given orally 50 mg twice a day. [91] It is not recommended for general use due to its adverse effects.

- Meclorethamine:

  Can cause hyper pigmentation of the skin after topical application by increasing the number of melanocytes.

- Levamisole:

  When given in a dose of 250mg for two consecutive days and every week for up to 48 months, was effective in controlling and reducing limited and slow spreading vitiligo.[92]

- TAR:

  Crude coal tar 300mg /ml was applied at weekly intervals to vitiligo macules and allowed to stay atleast for 3 hrs. 50% of patients found repigmentation after 10 to 30 cycles.[93]

OTHER SYSTEMIC AGENTS

- Calcium pantothenate 100mg along with Para amino benzoic acid (PABA) 500mg twice daily may help in repigmentation of vitiligo patches and leukotrichia associated with vitiligo. [94]

- Dapsone 100mg/day found to be useful in segmental vitiligo. [95] It probably acts by immunomodulation.

- Melatonin[96] has been found effective in vitiligo.

LASERS:

- EXCIMER LASER

  308 nm xenon lasers is an effective and safe modality for the treatment of stable vitiligo given twice or thrice weekly for 10 to 15 sittings.

- Ultrapulse CO2 laser used in association with PUVA therapy showed good results. [97]

Combination therapies:

Various combination therapies have been proved to be successful in the treatment of vitiligo. They are

- PUVA following surgical treatment .[98,99]
- NB-UVB with surgical therapies [100,101]
- Punch grafting with topical steroids (fluocinolone acetonide o.1%)[102]
- Topical steroids with 308 nm excimer laser [103] particularly helpful in difficult to treat areas such as bony prominences.
- Topical tacrolimus with NB-UVB [104]
- Oral antioxidants *Polypodium leucotomos* extract with NB-UVB. [105]

Depigmenting therapy for extensive vitiligo:

Indications:

- In case of extensive vitiligo refractory to treatment.
- To achieve a uniform appearance by removing islands of normal pigments in extensive vitiligo.

20% Monobenzyl ether of hydroquinone in a cream base is applied to the remaining areas of pigmentation twice daily for 3-6 months. It produces a permanent depigmentation.

Topical 20% 4-methoxy phenol can also be used for depigmentation\

Cryotherapy :

Cryospray application over a period of some weeks or months can cause the residual pigment to disappear without complications can be used for small areas but the patient must be tolerant to the discomfort produced during procedure.

SURGICAL MODALITIES FOR VITILIGO

- Therapeutic wounding: Dermabrasion, Laser ablation, LN cryosurgery, needling, Phenol or TCA application
- Cosmetic tattooing.
- Excision and closure
- Tissue graft:
  1. Thin and ultra-thin split-thickness skin grafts (STSG)
  2. Suction blister epidermal grafts (SBEG)
  3. Mini-punch grafts (MPG)
  4. Hair follicular grafts (HFG)
- Cellular graft:
  1. Non-cultured epidermal cell suspension (NCES)
  2. Cultured "pure" melanocytes (CM)
  3. Cultured epithelial grafts (CE)
  4. Ultrasonic abrasion and seed grafts [106]
  5. Flip-top technique of grafting [107]

Among all procedures, suction blister epidermal grafts, thin and ultra-thin split-thickness grafts seem to be the most effective procedure. Among cellular grafts, all techniques seem to be equally effective.

5 Fluorouracil and Dermabrasion

5 Fluorouracil:

It is a fluorinated pyrimidine antagonist which acts by interfering with DNA synthesis. Topical 5-fluorouracil (5-FU) has been used in clinical practice since 1960s.

Mechanism of Action:

It gets misincorporated in to RNA and disrupts its synthesis. The enzyme thymidilate synthetase is blocked by its metabolites thus interfering with DNA synthesis.

Adverse effects:

Localised :

- Erythema, irritation ,burning ,pain, pruritus ,hypo and hyperpigmentation , and allergic contact dermatitis

Systemic :

Systemic adverse effects are extremely rare with topical preparation.

The following adverse effects are noted with intravenous 5 FU

- Nausea, anorexia and diarrhea.
- Stomatitis, alopecia and myelosuppression.
- Cardiac and neurologic toxicity.

Unusual reactions:

This include onycholysis, onychodystrophy,and the appearance of telangiectasias.

AVAILABLE PREPARATIONS:

Available as a 0.5, 1 %, 2 % or 5% cream and 1% solution & 5% solution. The solution can also be used for intralesional iniection.

GENERAL THERAPEUTIC GUIDELINES FOR TOPICAL 5 FLUOROURACIL

Usual treatment duration is for 2- 6weeks and it has to be avoided in areas like nasolabial folds, and eyes. Treatment is restricted to 2 weeks in case of lesions over the face. Its inflammatory property produces edema, erythema & pain .Topical corticosteroids can be used concomitantly with 5 FU to relieve inflammation.

CLINICAL USE

INDICATIONS

- Actinic keratoses: 1 percent or 5 percent cream is FDA approved for treatment of actinic keratoses. 5-FU is used twice daily until an inflammatory response is seen, usually for 2 to 4 weeks. The 0.5% cream can be used once daily in case face and scalp lesions. 5 FU may also be a useful adjunct before cryosurgery of actinic keratoses.

- Squamous cell carcinoma in situ: 5% 5fluorouracil applied twice daily for 4-6 weeks.

- Porokeratosis: Found to be effective as once daily application without occlusion in treatment of multiple disseminated porokeratosis lesions[108,]
- Verrucae vulgaris, verrucae plana, plantar warts, and condylomata acuminate can be treated with topical and intralesional 5-FU.

Intralesional 5-Fluorouracil can also be used in case of Psoriasis and keratoacanthomas, infantile digital fibromatosis, keloids and hypertrophic scars.[109, 110]

In addition, actinic cheilitis, mucosal leukoplakia, radiodermatitis, Bowendisease, Bowenoid papulosis, and erythroplasia of Oueyrat have all been reported to respond to treatment with topical 5-FU.

5 Fluorouracil for vitiligo:

Various Studies have demonstrated therapeutic efficacy of topical 5% 5-FU, in the treatment of vitiligo with various success rates. [111,112,113]

Dermabrasion :

In this technique skin is abraded with an abrasive tip with high speed rotary hand engine manually or mechanically, that may be either a wire brush or a diamond fraise creating a wound that heals by secondary intention.

History of the Procedure:

The technique was first described by Kurtin in1953; he also described the use of high-speed rotary abraders, intraoperative freezing, and a variety of abrasive end pieces. Further refinement of this technique was done by Orentreich and Burks and Thomas. [114,115] Alt and Yarborough used the diamond fraise and wire brush respectively.

Mechanism of dermabrasion:

Dermabrasion removes the epidermis and papillary dermis thereby creating an open wound which heals by secondary intention. Stimulation of the inactive melanocytes at the outer root sheath of the hair following epidermal injury results in repigmentation in case of vitiligo.

TYPES OF DERMABRADORS:

They are of 2 types

1. Manual dermabrador
2. Mechanical dermabrador which uses either diamond fraise or wire brush to dermabrade the lesions.

Indications:

- Scars : Acne scars, post traumatic and surgical scars
- Rhinophyma,
- Deep rhytides
- Actinic Keratoses,
- Seborrheic keratosis.
- Angiofibromas,
- Syringomas
- Epidermal nevi,
- Stable Vitiligo [116]
- Pigmentary disorders like melasma,freckles,melanosis ,
- Tattoo removal.
- Hyperkeratotic lesions like lichen simplex chronicus,hypertrophic lichen planus, and lichen amyloidosis

Contraindication:

- Active herpetic lesions.
- Isotretinoin Therapy within 6-12 Months before procedure.
- Bleeding disorders.
- Immuno compromised individuals.

Preoperative evaluation:

Before starting the procedure one should look for patient's skin type, history of koebnerization, psychological status, history of keloidal tendency, systemic illness like diabetes to have better outcome.

Patient should be explained about the treatment, advantages, disadvantages and most importantly the realistic outcome of the procedure.

Clinical photographs taken before and after the procedure can be used as a tool to measure the improvement.

Role of Dermabrasion in vitiligo:

It can be used as a part of management of vitiligo in combination with other techniques.

- Epithelial sheet grafting following dermabrasion can be done.[117,118]
- Dermabrasion followed by thiersch grafting can induce repigmentation.
- Can be used in conjunction with thin split thickness skin grafting for effective repigmentation.[119,120]
- It can be used before transplantation of non cultured melanocytes.[121,122]

Disadvantage:

- Mainly operator dependent.
- Depth of penetration cannot be judged easily.

Complications:

- Transient, postoperative hyperpigmentation, usually seen 4-6 weeks after dermabrasion.
- 1/3 of patients develop hypopigmentation.
- Scar formation.
- Secondary Infections

Aim of the Study

AIM OF THE STUDY

The aim of the study is to evaluate the efficacy of dermabrasion with topical 1% 5-fluorouracil in patients with stable vitiligo patches and to assess the feasibility of this procedure in day to day practice.

Methodology

MATERIALS AND METHODS

This was a one year, open, prospective, study conducted in vitiligo patients attending Department of Dermatology, Coimbatore Medical College Hospital, Coimbatore. This study was conducted from June 2010 to June 2011. The procedure of dermabrasion with topical 5 fluorouracil was done for the patients within the first 6 months with follow up of the patient for next 6 months.

Twenty five patients, men and women, 15-60 years of age with clinical diagnosis of stable vitiligo of more than 2 year duration were eligible for enrollment in the study.

Name, age, sex, marital status, occupation, and residential address of the patients were noted.

A detailed history regarding the onset, duration and course of the disease, presence or absence of precipitating factors, family history, associated skin and systemic problems, treatment taken so far and its outcome were recorded. Dermatological assessment carried out mainly for the presence of white hairs.

INCLUSION CRITERIA

- Patients of both sexes.
- Age group between 15-60 years.
- Stable patches of vitiligo more than 2 year duration.

EXCLUSION CRITERIA

- Mucosal vitiligo, unstable vitiligo, actively spreading vitiligo
- Vitiligo less than 2 year duration.
- Children less than 12 years of age.
- Pregnant and lactating women.

- Diabetic patients.
- Patient currently under other topical or systemic therapy for vitiligo.
- Patients with keloidal tendency
- Patients with Bleeding Diathesis.
- H/o koebner phenonmenon.
- Vitiligo involving the face.

PRE OPERATIVE WORK-UP:

Once the criteria was satisfied informed written consent were obtained from the patient after explaining about the post procedure sequelae, side effects and complication. Screening for HIV was done in all patients in addition to complete hemogram, blood sugar, bleeding and clotting profile. Consent was obtained for taking photographs and they were instructed to come for regular follow-up.

PROCEDURE

A stable vitiligo patch was selected. Patch and the surrounding area were cleaned with spirit & povidone iodine solution, allowed to dry. 2% lignocaine injection was give intra dermally , after 10 mins of lignocaine infiltration , a hand held manual metallic dermabrador was used to dermabrade the patch initially in a to and fro motion, followed by horizontal and longitudional criss cross strokes, until pin point bleeding is seen in the patch. Surrounding skin within 1 cm area of the patch is also dermabraded to prevent recurrence. 1% 5-fluoruracil cream was applied over the patch to form a thin layer. Dermabraded site was closed with gauze and dressing done.

Patient was given systemic antibiotic for next 7 days and dressing was removed at the end of third day of the procedure. Patient was followed up at the end of every month for the next 6 months to look for repigmentation.

Photographs were taken before the procedure as well as during the follow up period. Any adverse effect during the study was recorded with importance to infection, pain & scarring.

Repigmentation was taken as,

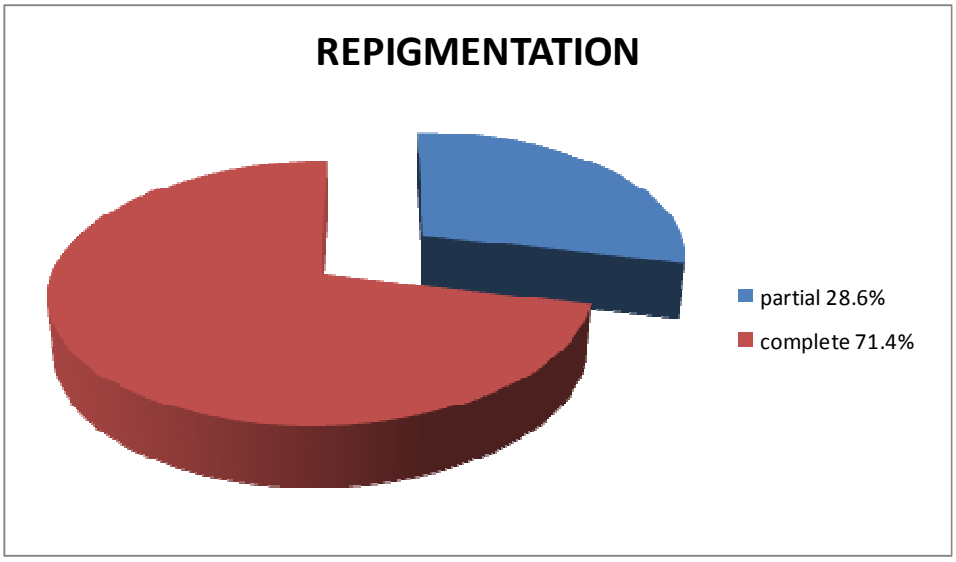
- Complete repigmentation when it was 100% and any percentage of pigmentation < 100 was taken as partial repigmentation

Observation and Results

OBSERVATION AND RESULT

Erythema pain and exudation over the abraded site has been noted for first 4-7 days in all the patients. After 1 week the patients were free from discomfort and pain. Perifollicular pigmentation has been noted at the end of first month in most of the patients. Secondary infection has been noted in only one patient that cleared after 1 week, after treating with antibiotics. Hyper pigmentation with scarring has been observed in three patients. At the at the end of 6 months out of 25 patients 4 did not turn for follow up. Partial repigmentation was observed in six patients (28.6%) and total repigmentation in fifteen patients (71.4%) .Of this complete repigmentation was seen at the end of third month in 7 patients & at the end of sixth month in 8 patients.

No of patients enrolled	No of patients came for regular follow up	No of patients showed complete repigmentation	No of patients with partial repigmentation	No of dropouts	Adverse effects noted			
25	21	15 (71.4%)	06 (28.57%)	04	Repigmentation noted were darker than normal skin in 13 patients (61.9%)	Superficial scar noted in 3(14..28 %) patients along with repigmentation	Secondary Infection noted in 1 patient	Pain at adraded site for a week noted in all 21(100%)Patients



Before Treatment

After Treatment

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Discussion

DISCUSSION

Dermabrasion with topical 5 fluorouracil was first used in vitiligo patients in 1983. It creates an epidermal injury that results in loss of integrity of the epidermis leading to stimulation of the inactive melanocytes at the outer root sheath of the hair which proliferate and migrate upwards and start synthesizing melanin at the infundibulum, from there they migrate and reach the surface of the skin that presents as perifollicular pigmentation , which enlarges to cover the depigmented area. Only pigmented hair acts as melanocytes reservoir for repigmentation hence the technique will not be useful in vitiligo patches with white hair.[123,124]

Once the epidermis has been removed, by applying topical 5 fluorouracil, an irritation is mediated that induce production of inflammatory cytokines and prostaglandins, which stimulate melanocyte migration and proliferation.

Two hypotheses postulated for fluorouracil induced repigmentation of vitiligo lesions are [125,126]

1. It stimulates the division of epidermal melanocytes that migrate into the affected areas after epithelialization of the epidermis or the melanocytes may be derived from the hair follicles

2. It competes with desoxyuridine and its derivatives for the enzyme thymidylate synthetase which is a potent inhibitor of a variety of cellular activities and kills some inhibitory agent or cells within the epidermis or dermis that were responsible for the destruction of the melanocytes causing vitiligo.

Repigmentation usually begins within two weeks after complete epithelialization of the wound. Only patients with stable disease and limited extension of the manifestations can be treated with this technique.

In our study complete repigmentation was seen in 15 patients out of 21 with 71.4% success rate for this procedure. A study done by Sethi et al comparing dermabrasion, dermabrasion with topical 5% 5-fluorouracil dressing, and dermabrasion with a topical placentrex gel, showed higher efficacy (73%) for the combined treatment of dermabrasion with 5- fluorouracil.[127]

Various studies have been done with either 5 fluorouracil or dermabrasion as well combination of both, in one study the effect of topical 5 fluorouracil ointment along with epidermal abrasion showed 81.5% success rate with dermabrasion along with 5 fluorouracil, 20.4% for topical 5 fluorouracil alone and 7.4% for dermabrasion alone .[128]

In our study 1% 5 fuorouracil cream was used while in previous studies, it was 5 % cream and therefore the severity of inflammation & side effects were minimal in our study.

In most of the previous studies, topical 5 fluorouracil was applied daily for a week ,whereas in our study it was applied for a short duration of 3 days under occlusion.

ADVANTAGES OF THIS PROCEDURE:

1. Single shot therapy.
2. Except for post procedure pain and discomfort no significant complications were noted in most of the patients.
3. Patient acceptance was good
4. Early repigmentation within 3 months of therapy.
5. Cost effective

LIMITATION OF THIS STUDY:

1. Small sample size
2. Repigmentation achieved were darker compared to normal skin but patient acceptance was good
3. It works only for stable vitiligo.
4. Not useful in mucosal, lip tip and acrofacial vitiligo

Conclusion

CONCLUSION

Among various surgical modalities available for vitiligo, dermabrasion along with 5 fluorouracil can be used as a simple office procedure, in repigmenting focal and to a lesser extent generalized stable vitiligo, which is very economical & brings early repigmentation without any significant side effects, which can allay the anxiety & stigma of the patients and brings back smile in their faces.

Proforma

PROFORMA

NAME:

Age :

Sex :

Address:

Occupation :

Clinical history:

Duration:

Family History :

H/o Diabetes:

H/o Bleeding tendancy:

H/o keloidal tendancy :

H/o suggestive of Koebner phenomenon :

Investigations:

Complete hemogram:

Blood

Urea:

Sugar:

Creatinine:

Bleeding time:

Clotting time:

Consent Form

Consent form

Hospital: Op number:

Patient name: Age/Sex:

Consent for surgical procedure:

I have been explained in language that I understand the nature of procedure, its expectected benefits, possible side effects and after effects and the risk involved.

After understanding all this things stated above I agree to undergo the above mentioned procedure.

Date: Signature of the patient

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